Refine Search

Search Results -

Terms	Documents
L1 same L2	6

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L6

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Friday, December 28, 2007 Purge Queries Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=NO; OP=OR			
L6	l1 same l2	6	L6
L5	l1 and l2	6	L5
L4	vhl or (von adj hippel adj lindau adj tumor adj suppressor)	2616	L4
L3	vhl or (von adj hippel adj lindau adj tumour adj suppressor)	2569	L3
L2	vdu1 or (vhl adj interacting adj deubiquitinase adj enzyme adj 1)	18	L2
L1	hif or (hypoxia adj inducible adj factor)	4038	L1

END OF SEARCH HISTORY

[File 5] **Biosis Previews(R)** 1926-2007/Dec W4

[File 6] **NTIS** 1964-2007/Dec W5

[File 8] **Ei Compendex(R)** 1884-2007/Dec W2

[File 24] **CSA Life Sciences Abstracts** 1966-2007/Aug

[File 34] **SciSearch(R) Cited Ref Sci** 1990-2007/Dec W5

[File 45] **EMCare** 2007/Dec W1

[File 65] **Inside Conferences** 1993-2007/Dec 28

[File 71] **ELSEVIER BIOBASE** 1994-2007/Dec W4

[File 73] **EMBASE** 1974-2007/Dec 21

**File 73: The file has been reloaded and accession numbers have changed. See HELP NEWS 72 for details.*

[File 98] **General Sci Abs** 1984-2007/Nov

[File 99] **Wilson Appl. Sci & Tech Abs** 1983-2007/Oct

[File 135] **NewsRx Weekly Reports** 1995-2007/Dec W5

[File 136] **BioEngineering Abstracts** 1966-2007/Jan

[File 143] **Biol. & Agric. Index** 1983-2007/Nov

[File 144] **Pascal** 1973-2007/Dec W2

[File 155] **MEDLINE(R)** 1950-2007/Nov 30

**File 155: MEDLINE has ceased updating with UD20071203. Please see HELP NEWS 154 for details.*

[File 172] **EMBASE Alert** 2007/Dec 12

[File 266] **FEDRIP** 2007/Oct

[File 315] **ChemEng & Biotec Abs** 1970-2007/Nov

[File 357] **Derwent Biotech Res.** _1982-2007/Nov W4

[File 358] **Current BioTech Abs** 1983-2006/Jan

**File 358: This file is no longer updating. Please use File 315, which includes all File 358 records and updates.*

[File 369] **New Scientist** 1994-2007/Sep W4

[File 370] **Science** 1996-1999/Jul W3

**File 370: This file is closed (no updates). Use File 47 for more current information.*

[File 399] **CA SEARCH(R)** 1967-2007/UD=14726

**File 399: Use is subject to the terms of your user/customer agreement. IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.*

[File 434] **SciSearch(R) Cited Ref Sci** 1974-1989/Dec

[File 40] **Enviroline(R)** 1975-2007/Oct

[File 41] **Pollution Abstracts** 1966-2007/Sep

[File 50] **CAB Abstracts** 1972-2007/Oct

[File 103] **Energy SciTec** 1974-2007/Nov B1

**File 103: For access restrictions see Help Restrict.*

[File 156] **ToxFile** 1965-2007/Nov W2

**File 156: Please see HELP NEWS 156 for information on changes to updating beginning in November.*

[File 162] **Global Health** 1983-2007/Oct

```
?  s vho or (von hippel lindau tumor suppressor)
          141   VHO
            2   VON HIPPEL LINDAU TUMOR SUPPRESSOR
S1        143   S VHO OR (VON HIPPEL LINDAU TUMOR SUPPRESSOR)

?  s vhu or (von hippel lindau tumor suppressor)
           48   VHU
            2   VON HIPPEL LINDAU TUMOR SUPPRESSOR
S2          50   S VHU OR (VON HIPPEL LINDAU TUMOR SUPPRESSOR)

?  rd
>>>W:  Duplicate detection is not supported for File 393.
Records from unsupported files will be retained in the RD set.
S3          28   RD  (UNIQUE ITEMS)

?  s hif or (hypoxia inducible factor)
        32750   HIF
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          368   HYPOXIA INDUCIBLE FACTOR
S4      32823   S HIF OR (HYPOXIA INDUCIBLE FACTOR)

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>>>W:  Duplicate detection is not supported for File 393.
Records from unsupported files will be retained in the RD set.
S5      13037   RD  (UNIQUE ITEMS)

?  s s3 and s5
           28   S3
        13037   S5
S6          1   S S3 AND S5
```

```
? show files
```

[File 5] **Biosis Previews(R)** 1926-2007/Dec W4

[File 6] **NTIS** 1964-2007/Dec W5

[File 8] **Ei Compendex(R)** 1884-2007/Dec W2

[File 24] **CSA Life Sciences Abstracts** 1966-2007/Aug

[File 34] **SciSearch(R) Cited Ref Sci** 1990-2007/Dec W5

[File 45] **EMCare** 2007/Dec W1

[File 65] **Inside Conferences** 1993-2007/Dec 28

[File 71] **ELSEVIER BIOBASE** 1994-2007/Dec W4

[File 73] **EMBASE** 1974-2007/Dec 21

**File 73: The file has been reloaded and accession numbers have changed. See HELP NEWS 72 for details.*

[File 98] **General Sci Abs** 1984-2007/Nov

[File 99] **Wilson Appl. Sci & Tech Abs** 1983-2007/Oct

[File 135] **NewsRx Weekly Reports** 1995-2007/Dec W5

[File 136] **BioEngineering Abstracts** 1966-2007/Jan

[File 143] **Biol. & Agric. Index** 1983-2007/Nov

[File 144] **Pascal** 1973-2007/Dec W2

[File 155] **MEDLINE(R)** 1950-2007/Nov 30

File 155: MEDLINE has ceased updating with UD20071203. Please see HELP NEWS 154 for details.

[File 172] **EMBASE Alert** 2007/Dec 12

[File 266] **FEDRIP** 2007/Oct

[File 315] **ChemEng & Biotec Abs** 1970-2007/Nov

[File 357] **Derwent Biotech Res.** _1982-2007/Nov W4

[File 358] **Current BioTech Abs** 1983-2006/Jan

File 358: This file is no longer updating. Please use File 315, which includes all File 358 records and updates.

[File 369] **New Scientist** 1994-2007/Sep W4

[File 370] **Science** 1996-1999/Jul W3

File 370: This file is closed (no updates). Use File 47 for more current information.

[File 399] **CA SEARCH(R)** 1967-2007/UD=14726

File 399: Use is subject to the terms of your user/customer agreement. IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.

[File 434] **SciSearch(R) Cited Ref Sci** 1974-1989/Dec

[File 40] **Enviroline(R)** 1975-2007/Oct

[File 41] **Pollution Abstracts** 1966-2007/Sep

[File 50] **CAB Abstracts** 1972-2007/Oct

[File 103] **Energy SciTec** 1974-2007/Nov B1

File 103: For access restrictions see Help Restrict.

[File 156] **ToxFile** 1965-2007/Nov W2

File 156: Please see HELP NEWS 156 for information on changes to updating beginning in November.

[File 162] **Global Health** 1983-2007/Oct

[File 305] **Analytical Abstracts** 1980-2007/Nov W4

**File 305: Alert feature enhanced for multiple files, duplicate removal, customized scheduling. See HELP ALERT.*

[File 393] **Beilstein Database - Abstracts** 2007/Q3

[File 35] **Dissertation Abs Online** 1861-2007/Aug

[File 91] **MANTIS(TM)** 1880-2007/Apr

**File 91: This database has stopped updating temporarily. Please see HELP NEWS 91 for details.*

[File 149] **TGG Health&Wellness DB(SM)** 1976-2007/Dec W1

[File 159] **Cancerlit** 1975-2002/Oct

**File 159: Cancerlit is no longer updating. Please see HELP NEWS159.*

[File 164] **Allied & Complementary Medicine** 1984-2007/Nov

[File 444] **New England Journal of Med.** 1985-2007/Nov W2

[File 467] **ExtraMED(tm)** 2000/Dec


```
; d s
Set     Items   Description
S1        143   S VHO OR (VON HIPPEL LINDAU TUMOR SUPPRESSOR)
S2         50   S VHU OR (VON HIPPEL LINDAU TUMOR SUPPRESSOR)
S3         28   RD  (unique items)
S4      32823   S HIF OR (HYPOXIA INDUCIBLE FACTOR)
S5      13037   RD  (unique items)
S6          1   S S3 AND S5
S7         51   S VDU1 OR (VHL INTERACTING DEUBIQUITINASE ENZYME 1)
S8         21   RD  (unique items)
S9          5   S S5 AND S8
```

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?  s vhl or (von hippel lindau tumor suppressor)
        11703   VHL
            2   VON HIPPEL LINDAU TUMOR SUPPRESSOR
S10     11705   S VHL OR (VON HIPPEL LINDAU TUMOR SUPPRESSOR)

?  s s10 and s9
        11705   S10
            5   S9
S11         4   S S10 AND S9
```

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 ; d s
Set     Items   Description
S1        143   S VHO OR (VON HIPPEL LINDAU TUMOR SUPPRESSOR)
S2         50   S VHU OR (VON HIPPEL LINDAU TUMOR SUPPRESSOR)
S3         28   RD  (unique items)
S4      32823   S HIF OR (HYPOXIA INDUCIBLE FACTOR)
S5      13037   RD  (unique items)
S6          1   S S3 AND S5
S7         51   S VDU1 OR (VHL INTERACTING DEUBIQUITINASE ENZYME 1)
S8         21   RD  (unique items)
S9          5   S S5 AND S8
 ; t /3,k/all
>>>W:  KWIC option is not available in file(s): 399
```

9/3,K/1 (Item 1 from file: 5) **Links**

Fulltext available through: USPTO Full Text Retrieval Options STIC Full Text Retrieval Options

Biosis Previews(R)

18317713 **Biosis No.:** 200510012213

VHLprotein-interacting deubiquitinating enzyme 2 deubiquitinates and stabilizes HIF-1 alpha

Author: Li Zaibo; Wang Dakun; Messing Edward M; Wu Guan (Reprint)
Author Address: Univ Rochester, Med Ctr, Dept Urol, 601 Elmwood Ave,Box 656, Rochester, NY 14642 USA**USA
Author E-mail Address: guanwu@urmc.rochester.edu

Journal: EMBO Reports 6 (4): p 373-378 APR 05 2005
ISSN: 1469-221X
Document Type: Article
Record Type: Abstract
Language: English

VHLprotein-interacting deubiquitinating enzyme 2 deubiquitinates and stabilizes HIF-1 alpha

Abstract: Hypoxia-inducible factor (HIF)-1 alpha is a short-lived protein and is ubiquitinated and degraded through the von... ...ubiquitination-related processes. Here, we show that pVHL-interacting deubiquitinating enzyme 2, VDU2, but not VDU1, interacts with HIF-1 alpha. VDU2 can specifically deubiquitinate and stabilize HIF-1 alpha and, therefore, increase expression of HIF-1 alpha targeted genes, such as vascular endothelial growth factor (VEGF). These findings suggest that ubiquitination of HIF-1 alpha is a dynamic process and that ubiquitinated HIF-1 alpha might be rescued from degradation by VDU2 through deubiquitination. Although pVHL functions as a master control for HIF-1 alpha stabilization, as pVHL-E3 ligase mediates the ubiquitination of both HIF-1 alpha and VDU2, the balance between the pVHL-mediated ubiquitination and VDU2-mediated deubiquitination of HIF-1 alpha provides another level of control for HIF-1 alpha stabilization.

DESCRIPTORS:

Chemicals & Biochemicals: ...hypoxia-inducible factor-1-alpha {HIF-1-alpha... ...deubiquitinating enzyme-1 {VDU1}

9/3,K/2 (Item 2 from file: 5) **Links**

Fulltext available through: USPTO Full Text Retrieval Options STIC Full Text Retrieval Options

Biosis Previews(R)

16819902 **Biosis No.:** 200200413413

Identification of a deubiquitinating enzyme subfamily as substrates of the von Hippel-Lindau tumor suppressor

Author: Li Zaibo; Wang Dakun; Na Xi; Schoen Susan R; Messing Edward M; Wu Guan (Reprint)

Author Address: Department of Urology, University of Rochester Medical Center, 601 Elmwood Ave., Box 656, Rochester, NY, 14642, USA**USA

Journal: Biochemical and Biophysical Research Communications 294 (3): p 700-709 June 14, 2002 2002

Medium: print

ISSN: 0006-291X

Document Type: Article

Record Type: Abstract

Language: English

Abstract: ...ligase complex which is involved in the ubiquitination and degradation of the alpha subunits of **HIF** (hypoxia-inducible factor) in the presence of oxygen. However, it is of considerable interest to identify pVHL substrates other than **HIF**. In our previous studies, we have shown that **VDU1** (pVHL-interacting deubiquitinating enzyme-1) can be ubiquitinated for rapid degradation in a pVHL-dependent... ...deubiquitinating enzyme-2), is a substrate of pVHL. Based on human and mouse cDNA sequences, **VDU1** and VDU2 are identical in approximately 59% of the amino acids with strong homology in... ...the signature motifs of the ubiquitin-specific processing protease family and possesses deubiquitinating activity. Like **VDU1**, VDU2 interacts with pVHL beta-domain and these two proteins can compete with each other... ...pVHL-dependent manner. Based on their amino acid sequence homology and functional interaction with pVHL, **VDU1** and VDU2 define a subfamily of ubiquitin specific processing proteases. Since deubiquitination, by reversing ubiquitination, has been recognized as an important regulatory step in ubiquitination-related processes, **VDU1** and VDU2 could be important substrates of pVHL E3 ligase complex.

DESCRIPTORS:

Gene Name: human **VDU1** gene (Hominidae... ...mouse **VDU1** gene (Muridae...

9/3,K/3 (Item 1 from file: 357) Links
Derwent Biotech Res.

0347040 **DBA Accession No.:** 2004-19332 **PATENT**
Identifying hypoxia inducible factor-alpha (HIF-alpha) modulators for treating e.g., inflammatory disease by determining the effect of the putative modulator on HIF-alpha stability or its ubiquitination state in a test system involving vector-mediated gene transfer and expression in host cell

Author: BERNARDS R; BRUMMELKAMP T R; DIRAC A M; NIJMAN S M
Patent Assignee: VER HET NEDERLANDS KANKER INST 2004
Patent Number: WO 200464711 **Patent Date:** 20040805 **WPI Accession No.:** 2004-571591 (200455)
Priority Application Number: GB 200313625 **Application Date:** 20030612
National Application Number: WO 2004EP408 **Application Date:** 20040116
Language: English
Identifying hypoxia inducible factor-alpha (HIF-alpha) modulators for treating e.g., inflammatory disease by determining the effect of the putative modulator on HIF-alpha stability or its ubiquitination state in a test system involving vector-mediated gene transfer...
Abstract: DERWENT ABSTRACT: NOVELTY - Assay for identifying modulators of hypoxia inducible factor-alpha (HIF-alpha) comprises: (1) bringing into contact a putative modulator and a vonhyppel-lindau (VHL)-interacting deubiquitinase enzyme 1 (VDU1); (2) determining if the modulator binds and/or modulates activity of VDU1; and (3) determining the effect of the putative modulator on HIF-alpha stability and/or on the ubiquitination state of HIF-alpha, in a test system comprising HIF-alpha and VDU1. DETAILED DESCRIPTION - Assay for identifying modulators of hypoxia inducible factor-alpha (HIF-alpha) comprises: (1) bringing into contact a putative modulator and a vonhyppel-lindau (VHL)-interacting deubiquitinase enzyme 1 (VDU1) polypeptide; (2) determining whether the putative modulator binds and/or modulates an activity of VDU1; and (3) determining the effect of the putative modulator on HIF-alpha stability and/or on the ubiquitination state of HIF-alpha, in a test system comprising HIF-alpha and VDU1. INDEPENDENT CLAIMS are also included for the following: (1) a modulator of VDU1 for use in a method of medical treatment; (2) treating a disease in which modulation of HIF is of therapeutic value; (3) a composition comprising the modulator of VDU1 and an excipient; (4) treating an individual having cylindromatosis; and (5) treating a disease associated... ...KB). BIOTECHNOLOGY - Preferred Method: The assay method for identifying modulators of hypoxia inducible factor-alpha (HIF-alpha) includes: (1) bringing into contact a VDU1 polypeptide with a putative modulator; (2) determining binding between the VDU1 polypeptide and the putative modulator; (3) bringing the putative modulator into contact with a test system comprising VDU1 and HIF-alpha; and (4) determining the effect of the putative modulator on the stability and/or state of ubiquitination of HIF-alpha. The assay method includes: (1) bringing into contact a VHL polypeptide, a VDU1 polypeptide and a putative modulator under conditions where the VHL polypeptide and the VDU1 polypeptide, in the absence of modulator, are capable of forming a complex; (2) determining whether the putative modulator modulates the interaction of the VHL and VDU1 polypeptides; (3) bringing the putative modulator into contact with a test system comprising VDU1, VHL and HIF-alpha; (4) determining the effect of the putative modulator on the stability and/or state of ubiquitination of HIF -alpha. The assay method includes: (1) bringing a putative modulator into contact with VDU1 and an ubiquitinated VDU1 substrate; (2) determining the ability of the putative modulator to modulate the stabilization and/or state of ubiquitination of the substrate by VDU1; (3) bringing the putative modulator into contact with a test system comprising VDU1 and HIF-alpha; (4) determining the effect of the putative modulator on the stability and/or state of ubiquitination of HIF-alpha. The assay method includes: (1) providing a cell culture in which cylindroma (CYLD) activity... ...The cell is under hypoxic or normoxic conditions. The effect of the putative modulator on

HIF-alpha stability is determined by the activity of a HIF-responsive reporter gene. The assay method includes: (1) bringing into contact a putative modulator with a test system comprising VDU1 and ubiquitinated HIF-alpha; and (2) determining the ability of the putative modulator to modulate the stabilization and/or state of ubiquitination of HIF-alpha by VDU1. The putative modulator is brought into contact with the test system under conditions where VDU1 is capable of stabilizing HIF-alpha, in the absence of the modulator. Treating a disease in which modulation of HIF is of therapeutic value comprises administering to an individual an agent which modulates the activity of VDU1. Treating an individual having cylindromatosis comprises administering to the individual a nuclear factor KB (NF... ...an agent which increases expression of CYLD. Preferred Modulator: The modulator is an antibody against VDU1. The modulator is a nucleic acid comprising a sequence encoding VDU1, such that when the modulator is present in a cell, VDU1 expression is enhanced. The modulator is an antisense RNA comprising a sequence which hybridizes to the VDU1 mRNA, a double stranded VDU1 RNA, or a ribozyme which targets VDU1 RNA, or which is a vector encoding the antisense RNA, double stranded RNA or ribozyme, such that when the modulator is present in a cell VDU1 expression is reduced. The modulator is a polypeptide having an amino acid sequence corresponding to a portion of the VHL or VDU1 amino acid sequence, and which binds specifically to VHL or VDU1 to prevent VHL and VDU1 from interacting. ACTIVITY - Antiarteriosclerotic; Antiarthritic; Antidiabetic; Antiinflammatory; Antipsoriatic; Antirheumatic; Cardiant; Cytostatic; Gynecological; Neuroprotective; Nootropic; Ophthalmological... ...given. USE - The assay method is useful for identifying modulators of hypoxia inducible factor-alpha (HIF-alpha). The modulator of VDU1 is useful for the manufacture of a medicament for treating a condition in which inhibition of HIF activity is of therapeutic value, e.g., inflammatory disease, cancer, macular degeneration and diabetic retinopathy... ...s disease, atherosclerosis, psoriasis, rheumatoid arthritis or endometriosis, or a condition in which activation of HIF is of therapeutic value, e.g., peripheral and coronary artery disease or myocardial ischemia. The...

9/3,K/4 (Item 1 from file: 399) **Links**
CA SEARCH(R)

141150973 **CA:** 141(10)150973p PATENT
Modulation of deubiquitinase family members
Inventor (Author): Bernards, Rene; Brummelkamp, Thijn R.; Dirac, Annette M.; Nijman, Sebastian M.
Location: Neth.
Assignee: Vereniging Het Nederlands Kanker Instituut
Patent: PCT International ; WO 200464711 A2 **Date:** 20040805
Application: WO 2004EP408 (20040116) *GB 20031124 (20030117) *GB 200313625 (20030612)
Pages: 67 pp.
CODEN: PIXXD2
Language: English
Patent Classifications:
Class: A61K-000/A
Designated Countries: AE; AE; AG; AL; AL; AM; AM; AM; AT; AT; AU; AZ; AZ; BA; BB; BG; BG; BR; BR; BW; BY; BY; BZ; BZ; CA; CH; CN; CN; CO; CO; CR; CR; CU; CU; CZ; CZ; DE; DE; DK; DK; DM; DZ; EC; EC; EE; EE; EG; ES; ES; FI; FI; GB; GD; GE; GE; GH; GM; HR; HR; HU; HU; ID; IL; IN; IS; JP; JP; KE; KE; KG; KG; KP; KP; KP; KR; KR; KZ; KZ; KZ; LC; LK; LR; LS; LS; LT; LU; LV; MA; MD; MD; MG; MK; MN; MW; MX; MX; MZ; MZ; NA; NI

9/3,K/5 (Item 1 from file: 35) **Links**
Dissertation Abs Online

01907745 ORDER NO: AADAA-I3064819

Identification of a ubiquitin specific processing protease subfamily as the downstream targets of thevon Hippel-Lindau tumor suppressor

Author: Li, Zaibo
Degree: Ph.D.
Year: 2002
Corporate Source/Institution: The University of Rochester (0188)
Source: Volume 6309B of Dissertations Abstracts International.
PAGE 4053 . 157 PAGES
ISBN: 0-493-83786-8

...VHL protein (pVHL) is a component of an E3 ubiquitin ligase. Hypoxia-inducible factor 1 (**HIF**-1) is a master regulator of oxygen homeostasis that controls angiogenesis, erythropoiesis, and glycolysis via ... ...proteins using yeast two-hybrid screening. A novel protein, named pVHL-interacting deubiquitinating enzyme 1 (**VDU1**), was identified as being able to directly interact with pVHL <italic>in vitro</italic> and... ...vivo</italic>. Sequence analysis reveals that the protein is well conserved between human and mouse. **VDU1** contains the signature motifs of the ubiquitin specific processing protease (UBP) family and possesses deubiquitinating activity as demonstrated by our enzymatic function studies. We show that **VDU1** interacts with pVHL β-domain, the substrate recognition region, and several naturally occurring mutations located in this domain disrupt their interaction. Finally, we demonstrate that **VDU1** can be ubiquitinated via a pVHL-dependent pathway for proteasomal degradation and <italic>VHL</italic> mutations that disrupt the interaction between **VDU1** and pVHL abrogate the ubiquitination of **VDU1**.

Through database searching, we found another uncharacterized deubiquitinating enzyme, named VDU2 (pVHL-interacting deubiquitinating enzyme 2), exhibiting a very high amino acid sequence homology with **VDU1**. To facilitate further sequence analysis, we determined a mouse homolog of VDU2. Based on human and mouse cDNA sequences, **VDU1** and VDU2 are identical in approximately 59% of the amino acids with strong homology in... ...a weaker similarity in the middle region. The pVHL interacting region is well conserved between **VDU1** and VDU2. VDU2 also contains the signature motifs of the ubiquitin-specific processing protease family and possesses deubiquitinating activity.

Our further investigations reveal that VDU2, but not **VDU1**, interacts with **HIF**-1α, an important downstream target of pVHL E3 ligase. More importantly, VDU2, a deubiquitinating enzyme, strongly stabilizes **HIF**-1α by deubiquitinating **HIF**-1α both <italic>in vitro</italic> and <italic> in vivo</italic>. These findings reveal that ubiquitination of **HIF**-1α is a dynamic process and that ubiquitinated **HIF**-1α can be rescued from degradation by VDU2 through direct deubiquitination. (Abstract shortened by...

/3,K/1 (Item 1 from file: 5) **Links**

Fulltext available through: USPTO Full Text Retrieval Options STIC Full Text Retrieval Options

Biosis Previews(R)

16570437 **Biosis No.:** 200200163948

von Hippel Lindau tumor suppressor and HIF-1alpha: New targets of NSAIDs inhibition of hypoxia-induced angiogenesis

Author: Jones Michael K; Szabo Imre L; Kawanaka Hirofumi; Husain Syeda S; Tarnawski Andrzej S (Reprint)

Author Address: DVA Medical Center, 5901 East Seventh St., Long Beach, CA, 90822, USA**USA

Journal: FASEB Journal 16 (2): p 264-266 February, 2002 2002

Medium: print

ISSN: 0892-6638

Document Type: Article

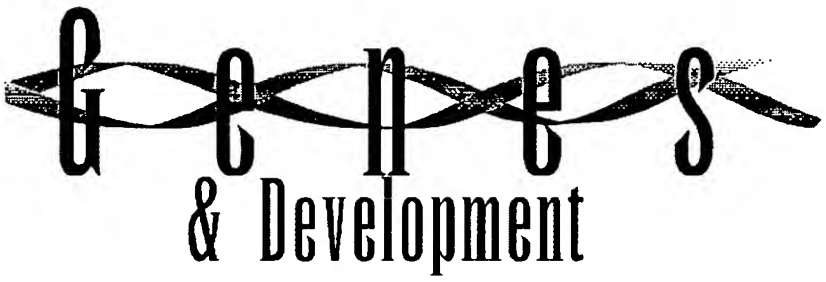
Record Type: Citation

Language: English

von Hippel Lindau tumor suppressor and HIF-1alpha: New targets of NSAIDs inhibition of hypoxia-induced angiogenesis

DESCRIPTORS:

Chemicals & Biochemicals: **...hypoxia-inducible transcription factor-1-alpha {HIF-1-alpha... ...von Hippel Lindau tumor suppressor**



HIF-1 and human disease: one highly involved factor

Gregg L. Semenza

Genes & Dev. 2000 14: 1983-1991
Access the most recent version at doi:10.1101/gad.14.16.1983

REVIEW

HIF-1 and human disease: one highly involved factor

Gregg L. Semenza[1]

Institute of Genetic Medicine, Departments of Pediatrics and Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287-3914 USA

Oxygen homeostasis represents an important organizing principle for human development and physiology. The essential requirement for oxidative phosphorylation to generate ATP is balanced by the risk of oxidative damage to cellular lipids, nucleic acids, and proteins. As a result, cellular and systemic O_2 concentrations are tightly regulated via short- and long-acting response pathways that affect the activity and expression of a multitude of cellular proteins (for review, see Semenza 1999a). This delicate balance is disrupted in heart disease, cancer, cerebrovascular disease, and chronic obstructive pulmonary disease, which represent the most common causes of mortality and account for two-thirds of all deaths in the U.S. (Greenlee 2000). Appreciation of the fundamental importance of oxygen homeostasis for development, physiology, and disease pathophysiology is growing but still incomplete. Knowledge acquisition is presently exponential when one includes areas, such as the role of angiogenesis in ischemic or neoplastic disease, in which investigators are studying oxygen homeostasis even though they may not interpret their studies within this broad physiological context.

Vascular endothelial growth factor (VEGF) plays an essential role in angiogenesis (for review, see Ferrara and Davis-Smyth 1997; Ferrara 1999). The regulation of VEGF expression illustrates how reduced O_2 availability (hypoxia) can elicit physiological responses via multiple molecular mechanisms. VEGF expression is induced when most cell types are subjected to hypoxia, thus providing a mechanism by which tissue perfusion can be optimized to demand. Steady state levels of *VEGF* mRNA increase in hypoxic cells as a result of increased production (transcriptional activation) and decreased destruction (mRNA stabilization). Whereas overall protein synthesis is inhibited in response to hypoxia, *VEGF* mRNA is efficiently translated into protein by use of an internal ribosome entry site (Stein et al. 1998). Finally, expression of the VEGF receptor FLT-1 is also induced when endothelial cells are exposed to hypoxia (Gerber et al. 1997).

The essential first step in this process, transcriptional activation, is mediated by the binding of hypoxia-inducible factor 1 (HIF-1) to a *cis*-acting hypoxia-response element located 1 kb 5′ to the transcriptional start site of the human *VEGF* gene (Forsythe et al. 1996). HIF-1 is a basic helix–loop–helix PAS protein consisting of HIF-1α and HIF-1β subunits (Wang and Semenza 1995; Wang et al. 1995). HIF-1α expression and HIF-1 transcriptional activity are precisely regulated by cellular O_2 concentration (for review, see Semenza 1999b, 2000a; Wenger 2000). The molecular mechanisms of sensing and signal transduction by which changes in O_2 concentration result in changes in HIF-1 activity are poorly understood, but recent data suggest that the O_2 signal is converted to a redox signal (Chandel et al. 2000; Haddad et al. 2000) that may trigger a kinase cascade and/or regulate HIF-1 directly (for review, see Semenza 1999a,b; Chandel and Schumacker 2000).

The regulation of HIF-1 activity occurs at multiple levels. Whereas HIF-1α mRNA is constitutively expressed in tissue culture cells, it is markedly induced by hypoxia or ischemia in vivo (Yu et al. 1998; Bergeron et al. 1999). HIF-1α protein expression is negatively regulated in nonhypoxic cells by ubiquitination and proteasomal degradation (Salceda and Caro 1997; Huang et al. 1998; Kallio et al. 1999). Under hypoxic conditions, HIF-1α protein levels increase dramatically and the fraction that is ubiquitinated decreases (Sutter et al. 2000). Nuclear localization of HIF-1α may also be induced by hypoxia (Kallio et al. 1998). The carboxy-terminal half of HIF-1α contains two transactivation domains that are also negatively regulated under nonhypoxic conditions (Jiang et al. 1997b; Pugh et al. 1997). The interaction of these domains with the coactivators CBP, p300, SRC-1, and TIF2 is regulated by the cellular O_2 concentration and redox state (Kallio et al. 1998; Ema et al. 1999; Carrero et al. 2000). Finally, species–specific alternative splicing of human and mouse HIF-1α RNA has also been reported (Wenger et al. 1997; Iyer et al. 1998b; Gothie et al. 2000). Hypoxia results in the rapid accumulation of HIF-1α in the nucleus (Wang et al. 1995) where it dimerizes with HIF-1β and binds to the core DNA sequence 5′-RCGTG-3′ (Semenza 2000a), leading to the transcriptional activation of *VEGF* and several dozen other known target genes (Table 1). HIF-1α and HIF-1β expression are required for embryonic survival in mice (Kozak et al. 1997; Maltepe et al. 1997; Iyer et al. 1998a; Ryan et al. 1998;

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Table 1. *Direct HIF-1 target genes*[a]

Glucose/Energy Metabolism and Cell Proliferation/Viability
Adenylate Kinase 3, Aldolase A, Aldolase C, Enolase 1 (ENO1), Glucose Transporter 1, Glucose Transporter 3, Glyceraldehyde-3-phosphate Dehydrogenase, Hexokinase 1, Hexokinase 2, Insulin-like Growth Factor 2 (IGF-2), IGF Binding Protein 1 (IGFBP-1), IGFBP-3, Lactate Dehydrogenase A, Phosphoglycerate Kinase 1, Pyruvate Kinase M, p21, Transforming Growth Factor β_3(TGFβ_3)
Erythropoiesis and Iron Metabolism
Ceruloplasmin, Erythropoietin, Transferrin, Transferrin Receptor
Vascular Development/Remodeling and Vasomotor Tone
α_{1B}-Adrenergic Receptor, Adrenomedullin, Endothelin-1, Heme Oxygenase 1, Nitric Oxide Synthase 2, Plasminogen Activator Inhibitor 1, Vascular Endothelial Growth Factor (VEGF), VEGF Receptor FLT-1
Other
$p35^{srg}$

[a]References for all HIF-1 target genes are cited in Semenza 2000b, except for TGFβ_3 (Caniggia et al. 2000) and ceruloplasmin (Mukhopadhyay et al. 2000).

Kotch et al. 1999). Proteins that are structurally related to HIF-1α (HIF-2α, HIF-3α) and HIF-1β (ARNT2, ARNT3) have been identified (for review, see Semenza 2000a) but their biological functions have not been established except for the finding that mice lacking HIF-2α (also known as EPAS1) die at midgestation because of catecholamine deficiency and heart failure (Tian et al. 1998). This review will focus on recent publications that have demonstrated involvement of HIF-1 in human disease pathophysiology.

Ischemic cardiovascular disorders

Myocardial ischemia

Atherosclerosis leads to arterial stenosis, impaired perfusion of the downstream vascular bed, and ischemia. When oxygen and glucose deprivation irreversibly affect myocardial viability, the end result is an infarction (heart attack). Hypoxia/ischemia has dramatic stimulatory effects on vascularization of coronary and peripheral vascular beds in fetal and juvenile animals whereas angiogenesis is markedly inhibited in aged animals because of impairment of VEGF production and endothelial cell responses to VEGF (Martin et al. 1998; Rivard et al. 1999). The impairment of VEGF production can be attributed to decreased HIF-1 activity in response to hypoxia (Frenkel-Denkberg et al. 1999; Rivard et al. 2000). Among middle-aged adults there is also variation in the extent to which ischemia induces the development of collateral blood vessels that allow perfusion of myocardium downstream of coronary artery stenosis and that influence the incidence and severity of myocardial infarction (Habib et al. 1991; Sabia et al. 1992). Myocardial ischemia induces VEGF expression (Banai et al. 1994) and the extent to which VEGF is induced in cultured leukocytes exposed to hypoxia ex vivo is correlated with the degree of coronary collateralization induced by myocardial ischemia in vivo (Schultz et al. 1999). HIF-1α mRNA and protein expression are induced and precede VEGF expression during acute ischemia and early infarction in the human heart (Lee et al. 2000). Thus, it is possible that variation in ischemia-induced HIF-1 activity may underlie the observed variation in VEGF expression and represent an important risk factor for myocardial infarction. In addition, therapeutic strategies designed to increase HIF-1α expression may promote angiogenesis within ischemic myocardium. PR39, a macrophage-derived peptide, has been shown to induce myocardial angiogenesis via inhibition of HIF-1α degradation (Li et al. 2000).

Ischemic preconditioning is an experimental phenomenon in which subjecting an animal to a sublethal ischemic challenge results in protection against a subsequent lethal challenge. There is an immediate but short-lived phase of protection within the first 2–3 hr that is followed by a delayed but sustained late phase of protection 12–24 hr later that requires new protein synthesis (Rizvi et al. 1999, and references therein). The late phase of ischemic preconditioning is lost in knockout mice that lack expression of the *Nos2* gene encoding inducible nitric oxide (NO) synthase (Guo et al. 1999). Induction of *Nos2* expression in hypoxic cardiac myocytes and vascular endothelial cells may be mediated by HIF-1 (Palmer et al. 1998; Jung et al. 2000). Furthermore, NO has been shown to induce HIF-1α expression under non-hypoxic conditions (Kimura et al. 2000). NO has been proposed to be both a trigger and a mediator of delayed preconditioning (Bolli et al. 1997). Thus, NO production in response to the preconditioning stimulus may induce HIF-1-mediated NOS2 expression that is protective against a subsequent lethal ischemic challenge. As in the case of ischemia-induced angiogenesis, once the molecular mechanisms of this process are more completely understood it may be possible to identify pharmacologic inducers that would have great therapeutic utility.

Cerebral ischemia

When adult rats are subjected to permanent middle cerebral artery occlusion, HIF-1α mRNA is induced in the penumbra or viable tissue surrounding the infarction (Bergeron et al. 1999). The induction of HIF-1α mRNA is temporally and spatially correlated with the expression of mRNAs encoding glucose transporter 1 and the glycolytic enzymes aldolase A, lactate dehydrogenase A, phosphofructokinase L, and pyruvate kinase M, which are all known HIF-1 target genes (Iyer et al. 1998a; Table 1). These data suggest that induction of glycolytic metabolism may promote the survival of neurons within the penumbra. Colocalization of HIF-1α and VEGF expression has also been demonstrated in the penumbra and is associated with neovascularization (Marti et al. 2000). In contrast, studies of primary cortical cultures from newborn mouse brains revealed that inhibition of

HIF-1 activity by overexpression of a dominant negative form of HIF-1α (Jiang et al. 1996) is associated with reduced cell death in response to oxygen and glucose deprivation (Halterman et al. 1999). Studies of HIF-1α-null embryonic stem cells also implicated HIF-1α in mediating apoptosis in response to oxygen and glucose deprivation (Carmeliet et al. 1998). These results are consistent with a model in which hypoxia-induced HIF-1α associates with and prevents the degradation of p53 protein (An et al. 1998), which then induces apoptosis of cortical neurons (Banasiak and Haddad 1998).

When newborn rats are subjected to permanent left common carotid artery occlusion and exposed to 8% O_2, cerebral infarction occurs in the hemisphere ipsilateral to the occlusion. Rats exposed to 8% O_2 for 3 hr and then subjected to carotid occlusion and hypoxia 24 hr later are protected against cerebral infarction (Gidday et al. 1994). As in the case of myocardial preconditioning (Bolli et al. 1997), cerebral preconditioning is blocked by NOS inhibitors (Gidday et al. 1999). Significant protection can also by achieved by injecting the rats with cobalt chloride or desferrioxamine (Bergeron et al. 2000), which are known inducers of HIF-1 activity (Wang and Semenza 1993). Exposure of rats to hypoxia alone induces HIF-1α protein expression throughout the brain, whereas combined carotid occlusion and hypoxia result in decreased HIF-1α expression in the ipsilateral cortex and a striking induction within the microvasculature of the ischemic brain (Bergeron et al. 2000). The physiological significance of this dramatic alteration in HIF-1α expression remains to be determined. In contrast to the data from in vivo studies suggesting that HIF-1α expression may contribute to hypoxic preconditioning, studies of cultured neurons suggest that hypoxic preconditioning ex vivo leads to decreased HIF-1α expression in response to oxygen-glucose deprivation 48 hr later (Ruscher et al. 1998). Thus, it will be important to definitively establish, for example, by analysis of partially HIF-1α-deficient mice (see below), whether the net effect of HIF-1α in vivo is protective or pathogenic and then to determine which cell types (glia, inflammatory cells, neurons) contribute to this effect.

Retinal ischemia

In diabetes, occlusion of retinal vessels leads to ischemia-induced neovascularization, which is a major cause of blindness. Clinical and laboratory studies have demonstrated a critical role of VEGF in this process (for review, see Ferrara 1999). In a mouse model of ischemic retinopathy, exposure of neonates to hyperoxia for five days results in vascular regression and retinal ischemia when the mice are returned to room air (Pierce et al. 1995), conditions similar to those that result in the retinopathy of prematurity. HIF-1α expression is induced during normal retinal development, is downregulated by hyperoxia, and upregulated on return to normoxic conditions, a pattern that is temporally and spatially correlated with VEGF expression (Ozaki et al. 1999).

Pulmonary hypertension

In some patients with chronic obstructive lung disease, alveolar hypoxia leads to the development of pulmonary hypertension. In this disorder, hypoxia-induced pulmonary arteriolar remodeling results in reduced lumen diameter and increased resistance to blood flow, leading to progressive right heart failure and, ultimately, patient death. Mice exposed to 10% O_2 for three weeks develop right ventricular hypertrophy as a result of increased right ventricular pressure, which is in turn secondary to medial wall hypertrophy within small pulmonary arterioles. This hypoxia-induced vascular remodeling is markedly impaired in mice that are heterozygous for a loss-of-function allele at the *Hif1a* locus and therefore partially HIF-1α deficient (Yu et al.1999). These results suggest that local inhibition of HIF-1 activity in the lung might represent a therapeutic strategy for treating or preventing pulmonary hypertension in at risk individuals.

Pregnancy disorders: preeclampsia and intrauterine growth retardation

Preeclampsia is a disorder of unknown etiology that affects 5% of all pregnancies and is a leading cause of fetal and maternal morbidity and mortality (for review, see Norwitz and Repke 2000; Roberts 2000). A central defect in preeclampsia appears to be the failure of trophoblasts to adequately invade the myometrium and induce remodeling of uterine spiral arteries during early placentation, which results in decreased uteroplacental perfusion (for review, see Aplin 2000). For most of the first trimester, the human fetus and placenta develop under hypoxic conditions but, at 10–12 weeks, the intervillous space opens and the placenta and fetus are exposed to maternal blood. It is at this stage that trophoblast cells actively invade the maternal decidua, and the developmental switch of trophoblasts from a proliferative to an invasive phenotype is controlled by the cellular O_2 concentration (Genbacev et al. 1996, 1997). The proliferative, noninvasive trophoblast phenotype appears to be maintained by hypoxia-induced, HIF-1-mediated expression of $TGF\beta_3$ because treatment of human villous explants with antisense oligonucleotides against HIF-1α or $TGF\beta_3$ induces invasion under hypoxic conditions (Caniggia et al. 2000). Inhibition of $TGF\beta_3$ also induces trophoblast invasion in explants from preeclamptic pregnancies (Caniggia et al. 1999), suggesting that defective downregulation of HIF-1α and/or $TGF\beta_3$ may play a major role in the pathogenesis of preeclampsia.

Another leading cause of fetal and neonatal morbidity and mortality is intrauterine growth retardation (IUGR). Decreased placental perfusion, resulting in placental and fetal hypoxia, is believed to be a major cause of IUGR. Fetal and maternal insulin-like growth factors (IGFs) play an important role in regulating fetal growth. IGF-binding protein 1 (IGFBP-1) is a negative regulator of IGF activity. IGFBP-1 expression, which is induced by hypoxia via a HIF-1 binding site in the gene promoter, is greatly increased in the cord blood of newborn children with IUGR (Tazuke et al. 1998).

Cancer

Hypoxia is an important selective force in the clonal evolution of tumors (Graeber et al. 1996) and HIF-1α is overexpressed in common human cancers (Zhong et al. 1999; Zagzag et al. 2000). The involvement of HIF-1 in tumor progression has been reviewed in detail (Semenza 2000b) but the major physiologic and genetic mechanisms leading to HIF-1α overexpression are summarized below.

Angiogenesis and hypoxia

Until primary tumors establish a blood supply, the limited diffusion of O_2 from nearby host vessels limits their growth to no more than a few cubic millimeters because cell division is balanced by cell death. Increased expression of VEGF is essential for the establishment of angiogenesis in most solid tumors. Experimental data (for review, see Semenza 2000b) suggest the following model: Increased VEGF expression is required to initiate and sustain tumor angiogenesis. Increased VEGF levels result from the synergistic effects of tumor hypoxia and tumor-specific genetic alterations (mutations) involving oncogenes and tumor suppressor genes. Increased VEGF expression results in the formation of dysfunctional vasculature that cannot adequately perfuse the entire tumor. Cellular adaptation to hypoxia is therefore a requirement of tumor progression independent of angiogenesis. As a result, most solid tumors have the seemingly paradoxical characteristic that poor clinical outcome is significantly correlated with both vascular density and tumor hypoxia.

In human gliomas, there is a significant association between tumor grade, vascularization, and HIF-1α overexpression (Zagzag et al. 2000). The highest grade glioma is glioblastoma multiforme (GBM), which is associated with a mean patient survival time of less than one year, regardless of treatment. In this condition, the rapidly proliferating tumor cells outstrip their blood supply resulting in extensive necrosis. The viable tumor cells surrounding necrotic regions express high levels of HIF-1α protein (Zhong et al. 1999; Zagzag et al. 2000) and *VEGF* mRNA (Plate et al. 1992; Shweiki et al. 1992). This pattern of expression suggests that the tumor cells are responding to hypoxia by HIF-1-mediated VEGF expression as demonstrated previously in cultured cells and mouse xenografts (Forsythe et al. 1996; Maxwell et al. 1997; Carmeliet et al. 1998; Iyer et al. 1998a; Ryan et al. 1998). GBMs have multiple mutations that inactivate tumor suppressor genes, including *p14ARF*, *p16CDKN2A*, *TP53*, and *PTEN* (Ishii et al. 1999), or activate oncogenes, including *CDK4*, *EGFR*, and *MDM2* (Holland et al. 1998). Remarkably, recent studies have established that mutations in oncogenes and tumor suppressor genes which had previously been shown to increase VEGF expression do so by induction of HIF-1, as described below.

Tumor suppressor genes

Hemangioblastoma is a brain tumor that differs from GBM by a lack of necrosis. This tumor is so well vascularized that, as its name implies, it was originally believed to arise from the progenitor cells for blood and vascular endothelial cells. Instead, hemangioblastomas produce extraordinarily high levels of VEGF that are responsible for inducing extensive vascularization. Remarkably, all hemangioblastomas analyzed overexpress HIF-1α (Zagzag et al. 2000). Hypoxia is unlikely to be a stimulus for HIF-1α expression in these cells. The key genetic lesion in hemangioblastoma and in clear cell renal carcinoma, another extensively vascularized tumor type, is functional inactivation of the von Hippel-Lindau (VHL) tumor suppressor (Gnarra et al. 1994; Herman et al. 1994; Kanno et al. 1994; Shuin et al. 1994). In renal carcinoma cell lines, VHL loss-of-function results in constitutive expression of HIF-1α under nonhypoxic conditions (Maxwell et al. 1999). VHL is associated with ubiquitin–protein ligase activity (Lisztwan et al. 1999) and loss of VHL function in renal carcinoma cells results in defective ubiquitination of HIF-1α under nonhypoxic conditions (Cockman et al. 2000).

p53 loss-of-function also leads to an increase in HIF-1α and VEGF expression that, although less dramatic than that associated with VHL loss-of-function, affects many more tumors, as loss of p53 activity occurs via one or more molecular mechanisms in the majority of human cancers (for review, see Giaccia and Kastan 1998). Remarkably, p53 also acts to target HIF-1α for ubiquitination but, in contrast to VHL, loss of p53 activity primarily leads to augmented hypoxia-induced HIF-1α and VEGF expression (Ravi et al. 2000). This is possible because there is considerable ubiquitination of HIF-1α even under hypoxic conditions (Sutter et al. 2000). HIF-1α and p53 directly interact, leading to the recruitment of the ubiquitin-protein ligase MDM2, which binds to p53 (Ravi et al. 2000). HIF-1α expression increases the stability of p53 (An et al. 1998) whereas p53 decreases the stability of HIF-1α in an MDM2-dependent manner (Ravi et al. 2000), suggesting that within the trimolecular complex HIF-1α is a preferential target of MDM2. HIF-1α-mediated stabilization of p53 may also play a role in hypoxia-mediated apoptosis leading to selection for loss of p53 function in tumor cells (Graeber et al. 1996).

Oncogenes

Dysregulation of signal transduction pathways regulating cell proliferation and viability is a hallmark of cancer. This can occur through gain-of-function mutations in genes encoding receptor tyrosine kinases such as EGFR, $HER2^{neu}$, or IGF-1R, and nonreceptor tyrosine kinases, such as c-SRC. The prototype oncogene, v-SRC, induces the expression of HIF-1α protein, HIF-1 DNA-binding and transcriptional activity, and mRNAs encoding VEGF and ENO1 (Jiang et al. 1997a). The biological effects of oncogenic tyrosine kinases occur via activation of the RAS, phosphatidylinositol-3-kinase (PI3K)/AKT (protein kinase B), and/or RAF/MEK/ERK (MAP kinase) pathways. In human prostate cancer cells, HIF-1α and VEGF overexpression are mediated via the PI3K/AKT pathway via the downstream effector kinase FKBP/rapa-

mycin-associated protein]FRAP; also known as mammalian target of rapamycin (mTOR)[(Zhong et al. 2000). Exposure of cells to LY294002 or rapamycin, inhibitors of PI3K and FRAP, respectively, completely blocks HIF-1α expression in nonhypoxic cells. In human prostate cancer and glioma cell lines, HIF-1-dependent transcription can be induced by a constitutively active form of AKT or a dominant-negative form of the phosphatase PTEN, which functions as a tumor suppressor by negatively regulating the PI3K/AKT pathway (Zhong et al. 2000; Zundel et al. 2000). PTEN loss of function is correlated with angiogenesis and advanced tumor stage in human prostate cancer (Giri and Ittmann 1999; McMenamin et al. 1999). Overexpression of PTEN in glioma cells dramatically reduces the accumulation of HIF-1α (Zundel et al. 2000), suggesting that the PI3K/AKT pathway may also regulate the ubiquitination of HIF-1α.

Oncogenic RAS mutations are also very common in human cancer and can lead to VEGF expression via either the PI3K or MAPK pathway, depending upon the cell type (Rak et al. 2000). The induction of VEGF promoter activity in H-RAS-transformed NIH 3T3 cells is dependent on PI3K (but not FRAP) activity and the presence of an intact HIF-1-binding site (Mazure et al. 1997). In CCL-39 fibroblasts, expression of RAF-1 results in phosphorylation of HIF-1α by p42 and p44 ERK, which is associated with increased HIF-1 transcriptional activity but no increase in HIF-1α protein expression (Richard et al. 1999), suggesting an effect on transactivation domain function, but the site of phosphorylation has not been reported. HIF-1α may also be phosphorylated by ERK in HMEC-1 endothelial cells under hypoxic conditions (Minet et al. 2000). Exposure of mouse embryonic fibroblasts to the organomercurial compound mersalyl induces the expression of HIF-1α protein, HIF-1 DNA-binding and transcriptional activity, and mRNAs encoding VEGF and ENO1, an effect that is dependent on the presence of IGF-1R and MEK activity (Agani and Semenza 1998). These studies suggest that the MAP kinase pathway can regulate HIF-1α protein stabilization or transactivation in a cell-type or stimulus-specific manner.

Effects of increased HIF-1 activity on tumor biology

Taken together, recent data indicate that HIF-1 activity is increased by both physiologic and epigenetic mechanisms in human cancer. Analysis of isogenic cell lines in nude mouse xenograft assays indicate that loss of HIF-1 activity results in increased tumor latency and decreased vascular density (Jiang et al. 1997a; Maxwell et al. 1997; Carmeliet et al. 1998; Ryan et al. 1998), whereas overexpression of HIF-1α results in decreased tumor latency and increased vascular density, volume, and permeability (Ravi et al. 2000). Known HIF-1 target genes provide a molecular basis by which HIF-1 overexpression may promote key aspects of tumor progression (Table 1): Glucose transporters and glycolytic enzymes promote metabolic adaptation to hypoxia; NOS2 and VEGF promote angiogenesis; IGF-2 promotes cell survival and proliferation. Novel therapeutic strategies designed to exploit the decreased O_2 concentration or increased HIF-1 expression within tumors are presently being evaluated (Dachs et al. 1997; Brown 2000; Shibata et al. 2000).

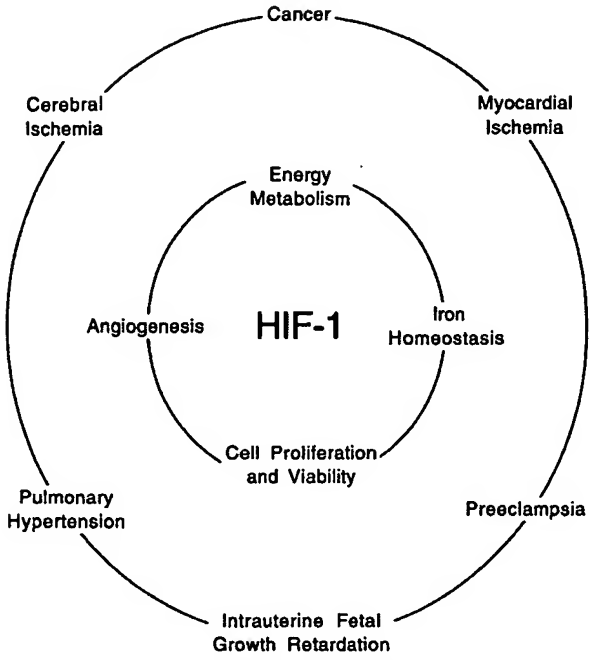

Figure 1. Involvement of HIF-1 in key physiological and pathophysiological processes. HIF-1 participates in essential developmental and physiological processes (inner circle) via transactivation of target genes (see Table 1). HIF-1 transactivation of target genes also contributes to either protective or pathologic responses in several major disease states (outer circle) as described in the text.

Conclusion

Data regarding the involvement of HIF-1 in developmental, physiological, and pathophysiological processes (Fig. 1) are presently accumulating at an exponential rate. Potential clinical applications of this knowledge will be dependent on continued scientific progress in three general areas: delineation of the complex cell-type- and stimulus-specific mechanisms by which HIF-1 activity is regulated; characterization of the target genes and biological processes that are regulated by HIF-1 within a given cell type and (patho)physiological state; and development of technology for efficient cell-type-specific targeting of DNA- and small-molecule-based therapeutics.

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